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Advances in Neuropathic Pain

Diagnosis, Mechanisms, and Treatment Recommendations

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Chronic neuropathic pain, caused by lesions in the peripheral or central nervous system, comes in many forms. We describe current approaches to the diagnosis and assessment of neuropathic pain and discuss the results of recent research on its pathophysiologic mechanisms. Randomized controlled clinical trials of gabapentin, the 5% lidocaine patch, opioid analgesics, tramadol hydrochloride, and tricyclic antidepressants provide an evidence-based approach to the treatment of neuropathic pain, and specific recommendations are presented for use of these medications. Continued progress in basic and clinical research on the pathophysiologic mechanisms of neuropathic pain may make it possible to predict effective treatments for individual patients by application of a pain mechanism–based approach.

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Chronic neuropathic pain is common in clinical practice. Patients with conditions as diverse as diabetic polyneuropathy, human immunodeficiency virus (HIV) sensory neuropathy, poststroke syndromes, and multiple sclerosis frequently experience daily pain that greatly impairs their quality of life. **Table 1** divides common chronic neuropathic pain syndromes into 2 groups based on a central or peripheral location of the nervous system lesion. It is probable, however, that both peripheral and central nervous system mechanisms contribute to the persistence of most types of neuropathic pain. Although precise estimates of the prevalence of neuropathic pain are not available, it is more common than has generally been appreciated. In the United States, there may be more than 3 million people with painful diabetic neuropathy (PDN)[1] and as many as 1 million with postherpetic neuralgia (PHN).[2]

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An evidence-based treatment approach is becoming feasible as the number of published randomized controlled trials continues to grow steadily. In this article, we discuss the diagnosis and assessment of neuropathic pain and survey recent research on pathophysiologic mechanisms. Evidence-based treatment recommendations for the pharmacologic management of chronic neuropathic pain are presented that take into account clinical effectiveness, adverse effects, influence on quality of life, and cost.

Author affiliations and financial disclosures are listed at the end of this article.

DIAGNOSIS AND ASSESSMENT

Neuropathic pain syndromes typically have both negative and positive sensory symptoms and signs.[3] Nonsensory neurological symptoms and signs depend on the underlying cause and may independently contribute to pain and disability. Although neuropathic pain has been defined by the International Association for the Study of Pain as pain "initiated or caused by a primary lesion or dysfunction in the nervous system,"[4(p212)] several investigators have recently argued that the inclusion of the term *dysfunction* makes this definition vague and unacceptably broad.[5,6] A proposed solution is to define neuropathic pain as pain caused by a lesion of the peripheral or central nervous

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system (or both) manifesting with sensory symptoms and signs.[6] Underlying causes include infections, trauma, metabolic abnormalities, chemotherapy, surgery, irradiation, neurotoxins, inherited neurodegeneration, nerve compression, inflammation, and tumor infiltration. Demonstrating a lesion of the nervous system compatible with particular symptoms and signs provides strong support for considering the pain to be neuropathic. However, when no lesion can be demonstrated, the limits of current diagnostic technology do not always allow the possibility of neuropathic pain to be excluded. The diagnosis of neuropathic pain is based on a medical history, review of systems, physical and neurological examination, and appropriate laboratory studies including blood and serologic tests, magnetic resonance imaging, and electrophysiologic studies.[3] In some instances, nerve or skin biopsy is necessary to directly visualize nerve fibers.

Table 1. Common Types of Neuropathic Pain

Peripheral neuropathic pain
Acute and chronic inflammatory demyelinating polyradiculoneuropathy
Alcoholic polyneuropathy
Chemotherapy-induced polyneuropathy
Complex regional pain syndrome
Entrapment neuropathies (eg, carpal tunnel syndrome)
HIV sensory neuropathy
Iatrogenic neuralgias (eg, postmastectomy pain or postthoracotomy pain)
Idiopathic sensory neuropathy
Nerve compression or infiltration by tumor
Nutritional deficiency–related neuropathies
Painful diabetic neuropathy
Phantom limb pain
Postherpetic neuralgia
Postradiation plexopathy
Radiculopathy (cervical, thoracic, or lumbosacral)
Toxic exposure–related neuropathies
Tic douloureux (trigeminal neuralgia)
Posttraumatic neuralgias
Central neuropathic pain
Compressive myelopathy from spinal stenosis
HIV myelopathy
Multiple sclerosis–related pain
Parkinson disease–related pain
Postischemic myelopathy
Postradiation myelopathy
Poststroke pain
Posttraumatic spinal cord injury pain
Syringomyelia

Abbreviation: HIV, human immunodeficiency virus.

Evaluation of Pain and Other Symptoms

The assessment of pain and other symptoms is needed for diagnosis and to guide therapy. No single symptom or sign is pathognomonic. Because neuropathic pain is the result of disease or injury to the nervous system, clinical manifestations typically include both negative and positive sensory symptoms and signs. Motor symptoms and signs are often present, but these deficits can be very subtle.

A distinction should be made between stimulus-evoked pain and spontaneous (stimulus-independent) pain, which may have different underlying mechanisms.[7] Spontaneous pain can be either constant or intermittent (even paroxysmal), and most patients describe having both (eg, constant "burning" pain plus intermittent pain that is "shooting" or "electric shock–like"). In addition, spontaneous paresthesias and dysesthesias manifest as abnormal sensations, including crawling, numbness, itching, and tingling. When obtaining the patient's history, it is important to assess the intensity, quality, and duration of spontaneous pain and abnormal sensations. The topographical distribution is especially helpful in guiding the neurological examination.

Pain may be evoked by everyday environmental stimuli such as the gentle touch and pressure of clothing, wind, riding in a car, and hot and cold temperatures. Common neurological examination tools, including a cotton wisp, a foam brush, a tuning fork, and cold and warm water–filled tubes, can be used to mimic these stimuli.

Pain intensity can be rated with any of several reliable and validated verbal, numerical, or visual analog scales. Patients rate their pain using some type of continuum (eg, "no pain" to "worst possible pain").[8] The often unusual abnormal sensations in patients with neuropathic pain can be assessed with measures of pain quality such as the Neuropathic Pain Scale[9] and Neuropathic Pain Questionnaire.[10] Chronic pain has a significant negative effect on quality of life, and various measures of physical and emotional function can also be used to evaluate a patient's response to treatment.[11] Assessment of psychological comorbidity (eg, depression or anxiety), sleep disturbance, work-related issues, treatment expectations, rehabilitative needs, and the availability of social support from family and friends should not be overlooked.[12]

Physical Examination

A thorough physical and neurological examination can help determine where the lesion is and assess nonneuropathic contributions to the patient's pain, most commonly musculoskeletal, inflammatory, myofascial, and psychological processes.[3] When combined with a history and laboratory tests suggesting a specific cause, the finding of negative and positive sensory phenomena in the same area innervated by damaged nervous system pathways usually confirms the diagnosis.

Patients may have sensory deficits with one modality, such as pinprick sensitivity, and hyperalgesia to another, such as light touch, in the same nerve distribution. Whereas the physician may have difficulty recognizing this paradoxical finding, patients are even more confused by the complexity of their sensory experiences; they often have trouble describing the unusual nature of their symptoms and fear that they will not be believed. For patients to be good sensory witnesses and provide all of the necessary information, they need to be reassured as well as instructed to carefully describe their symptoms and rate the severity of their abnormal sensations. When specific stimuli in the standard neurological sensory examination are applied first to the unaffected area and then to the area affected by pain, patients

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should be instructed to first respond in simple terms—that is, whether the stimulus applied to the painful area causes the same sensation as in the unaffected area or whether it is less or more intense—before describing their perception of the quality of the stimulus. For example, pinprick may be more painful (hyperalgesia) but less sharp because of the underlying sensory deficit.

Pain in response to a normally nonnoxious stimulus is termed *allodynia*. Dynamic mechanical allodynia can be elicited by lightly rubbing or brushing the skin with a cotton swab or brush, static mechanical allodynia can be provoked by blunt pressure with a finger, and thermal allodynia can be assessed with a warm or cool tuning fork. An increased sensation of pain in response to a normally painful stimulus is termed *hyperalgesia*, which can be assessed using painful thermal (cold or heat) or punctate (eg, pinprick) stimuli. Painful summation and hyperpathia to repeated stimuli, especially when the initial sensation is reduced, is important evidence of abnormal sensory processing.

Nonsensory neurological and musculoskeletal symptoms may contribute strongly to overall disability. Motor system symptoms and signs include weakness, fatigability, hypotonia, tremor, dystonia, spasticity, ataxia, apraxia, and motor neglect. Other musculoskeletal symptoms and signs include decreased range of motion, stiffness of joints, spontaneous muscle spasms, localized muscle tenderness, and myofascial trigger points.

Ancillary Studies

There is no single diagnostic test for neuropathic pain or pain in general. Ancillary studies can confirm or exclude underlying causes and suggest disease-specific treatments, such as for diabetes mellitus in patients with painful neuropathy or spinal disorders in patients with radiculopathy. To assess peripheral nerve function, nerve conduction velocity tests and electromyography provide information about large myelinated peripheral nerve function but do not test smaller myelinated or unmyelinated nerve fibers carrying pain and temperature information. Quantitative thermal sensory testing relies on the patient's psychophysical ability to discriminate between fine changes in thermal stimuli; it is not widely used because it requires specialized equipment and training. Magnetic resonance imaging assesses anatomical integrity of thermonociceptive sensory-processing regions such as the brainstem, thalamus, sensory cortex, anterior cingulate, and insular cortex, which can contribute to central neuropathic pain when injured. Functional magnetic resonance imaging can further assess these and other pain-related structures, but its role in clinical practice will remain limited in the near future.

Diagnosing neuropathic pain can be difficult. For example, in radicular neck and low back pain, there is a significant neuropathic component from the nerve root injury, but mechanical instability or secondary myofascial pain may mask this component. Physicians should also keep in mind that psychosocial factors are a major component of the experience of chronic pain and should be routinely addressed when patients are evaluated. Psychological processes such as anxiety can influence the report of pain and in rare instances produce exaggerated responses. However, sincerely communicating that the patient's pain is taken seriously and providing clear instructions will minimize the possibility that the neurological examination is unreliable or uninterpretable because of psychological processes. When combined with a long history of multiple unexplained pain problems, somatization disorder or another psychiatric diagnosis is possible. Proper diagnosis is the cornerstone of effective treatment, and complex patterns of signs and symptoms may necessitate the involvement of multiple medical specialties.

PATHOPHYSIOLOGIC MECHANISMS

Our ability to translate pain complaints and sensory findings into specific pathophysiologic mechanisms that have treatment implications is in its infancy.[13-16] Clinical investigations of pain mechanisms are labor intensive and require specialized equipment; thus, they are not yet practical for routine clinical use. Even in specialized pain research settings, it is difficult to identify specific neuropathic pain mechanisms. A simple focal peripheral nerve injury unleashes a range of peripheral and central nervous system processes that can all contribute to persistent pain and abnormal sensation. Inflammation, reparatory mechanisms of neural tissues in response to injury, and the reaction of adjacent tissues to injury lead to a state of hyperexcitability in primary afferent nociceptors, a phenomenon termed *peripheral sensitization*. In turn, central neurons innervated by such nociceptors undergo dramatic functional changes including a state of hyperexcitability termed *central sensitization*. Normally these sensitization phenomena extinguish themselves as the tissue heals and inflammation subsides. However, when primary afferent function is altered in an enduring way by injury or disease of the nervous system, these processes persist and may be highly resistant to treatment.

Injury or permanent loss of primary afferent fibers (deafferentation) differentiates peripheral neuropathic pain from other types of pain. Positive sensory phenomena (spontaneous pain, allodynia, and hyperalgesia) that are characteristic of patients with neuropathic pain are likely to have many underlying mechanisms, including ectopic generation of impulses as well as the de novo expression of neurotransmitters and their receptors and ion channels. Direct injury to central structures may permanently alter sensory processing, and in some patients it causes central neuropathic pain and dysesthesias. The mechanisms underlying central neuropathic pain, however, are still unclear.

An oversimplified but useful approach is to distinguish processes that involve the following: (1) increased primary afferent nociceptor firing (eg, as a result of abnormal collections of sodium channels in damaged peripheral nerve fibers, causing ectopic discharge); (2) decreased inhibition of neuronal activity in central structures (eg, due to loss of inhibitory neurons); and (3) altered central processing (central sensitization) so that normal sensory input is amplified and sustained. A continuum that has been explored in PHN has "irritability" of the nociceptive system at one end and

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deafferentation at the other.[15,16] Although the ends of the continuum can be differentiated by clinical examination and response to a brief focal application of topical capsaicin (capsaicin response test), the treatment implications of this differentiation remain to be explored.[17] The contributions of other peripheral processes remain poorly understood. For example, the sympathetic nervous system may facilitate persistent abnormal primary afferent nociceptor activity following nerve injury,[18] and nerve injury and inflammation during the acute phase of herpes zoster may be followed by a mixture of abnormal regeneration and receptor expression and permanent cutaneous afferent loss in patients with PHN.[19]

Although the many mechanisms identified in animal models of neuropathic pain still require translation and confirmation in human neuropathic pain syndromes, the results from these models provide valuable insights into diverse manifestations of neuropathic pain. Human laboratory studies,[20-22] although limited in number, support the idea that the pathophysiologic mechanisms discovered in animal models are relevant to our understanding of human neuropathic pain.

TREATMENT RECOMMENDATIONS

Members of the faculty of the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain participated in a meeting supported by an unrestricted educational grant to the University of Rochester Office of Professional Education (Rochester, NY) from Endo Pharmaceuticals (Chadds Ford, Pa) and contributed as authors to the preparation of this article. Specialties represented include anesthesiology, basic neuroscience, epidemiology, geriatrics, internal medicine, neurology, neurosurgery, outcomes research, pharmacoeconomics, and psychology. MEDLINE searches, examination of reference lists of published articles and book chapters, and personal knowledge of the literature were used to identify material relevant to developing treatment recommendations for patients with neuropathic pain. This material included systematic literature reviews, reports of randomized clinical trials, and publications discussing the development and evaluation of clinical guidelines.

General Considerations

To evaluate changes in pain intensity during treatment, an 11-point numerical rating scale in which 0 equals "no pain" and 10 equals "worst possible pain" is widely used to assess the patient's level of pain currently, during the past day, or during the past week. Recent data suggest that a reduction of 30% on such a scale is clinically important and equivalent to categorical ratings of "moderate relief" or "much improved."[23] The first-line treatments discussed as follows have all been demonstrated to provide statistically significant and clinically meaningful treatment benefits compared with placebo in multiple randomized controlled trials. Benefits of pharmacotherapy for improving quality of life, including physical and emotional function, have been found less consistently than for reducing pain intensity. Although the efficacy of treatments have been compared by evaluating the number needed to treat,[24-28] the small sample sizes and methodological shortcomings of some trials limit confidence in such comparisons.

Drug-related adverse effects are common in the treatment of neuropathic pain, not only because of the specific medications used but also because many patients with this condition are older, take other medications, and have comorbid illnesses. On the basis of our clinical experience and analyses of the number needed to harm,[24,25,27] we considered safety, adverse effects, and drug interactions in the development of our recommendations.

Most randomized controlled trials of chronic neuropathic pain have examined only 2 pain syndromes, PDN and PHN. Moreover, the US Food and Drug Administration (FDA) has approved medications for the treatment of only 2 specific neuropathic pain syndromes: trigeminal neuralgia (carbamazepine) and PHN (gabapentin and the 5% lidocaine patch). The applicability of the results of clinical trials for one chronic neuropathic pain syndrome to others cannot be determined, but most of the first-line therapies discussed as follows have been tested with multiple types of neuropathic pain and have shown similar results.[26] Medications with minimal risk that have demonstrated efficacy for 1 or more (ideally related) neuropathic pain syndromes are preferred. When efficacy has not been established, acceptable safety and tolerability in light of the patient's medical condition, age, pain severity, and previous treatment history are paramount.

Five caveats are required before presenting our treatment recommendations. First, these recommendations may apply to complex regional pain syndrome type I, although controlled trials of first-line medications are lacking; this pain syndrome is believed to be due to nervous system dysfunction without permanent injury to a nerve trunk. Second, although chronic neuropathic back pain (ie, cervical and lumbar radiculopathic pain) is probably the most prevalent pain syndrome to which neuropathic mechanisms contribute, there are no accepted diagnostic criteria for identifying this neuropathic component. It is likely that a combination of neuropathic, skeletal, and myofascial mechanisms account for this type of pain in many patients. Subgroup analyses of a randomized placebo-controlled trial suggested that patients who had chronic radicular low back pain responded best to treatment with nortriptyline hydrochloride,[29] one of the first-line medications discussed as follows. Third, distinct treatment guidelines for tic douloureux (trigeminal neuralgia) emphasize carbamazepine, phenytoin, and baclofen.[30] Fourth, we acknowledge that pharmacologic management is not a cure and should be considered an integral component of a more comprehensive approach to treatment. A discussion of the many widely used nonpharmacologic approaches including physical therapy, psychological treatments, invasive procedures (eg, neural blockade or dorsal column stimulation), and various complementary and alternative medicine interventions is beyond the scope of this review. Fifth, we assume that pharmacotherapy will be used within a treatment context in which education, support, and reassurance characterize the relationship between the patient and physician. We strongly rec-

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Table 2. First-line Medications for Neuropathic Pain

Medication	Beginning Dosage	Titration	Maximum Dosage	Duration of Adequate Trial
Gabapentin	100-300 mg every night or 100-300 mg 3 times daily	Increase by 100-300 mg 3 times daily every 1-7 d as tolerated	3600 mg/d (1200 mg 3 times daily); reduce if low creatinine clearance	3-8 wk for titration plus 1-2 wk at maximum tolerated dosage
5% Lidocaine patch	Maximum of 3 patches daily for a maximum of 12 h	None needed	Maximum of 3 patches daily for a maximum of 12 h	2 wk
Opioid analgesics*	5-15 mg every 4 h as needed	After 1-2 wk, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed	No maximum with careful titration; consider evaluation by pain specialist at dosages exceeding 120-180 mg/d	4-6 wk
Tramadol hydrochloride	50 mg once or twice daily	Increase by 50-100 mg/d in divided doses every 3-7 d as tolerated	400 mg/d (100 mg 4 times daily); in patients older than 75 y, 300 mg/d in divided doses	4 wk
Tricyclic antidepressants (eg, nortriptyline hydrochloride or desipramine hydrochloride)	10-25 mg every night	Increase by 10-25 mg/d every 3-7 d as tolerated	75-150 mg/d; if blood level of active drug and its metabolite is <100 ng/mL, continue titration with caution	6-8 wk with at least 1-2 wk at maximum tolerated dosage

*Dosages given are for morphine sulfate.

ommend that the dosage be adjusted as necessary based on frequent and careful evaluation of adverse effects, treatment adherence, and pain relief.

Review and Specific Recommendations

Recommendations for first-line pharmacologic treatments are based on positive results from multiple randomized controlled trials, and recommendations for second-line pharmacologic treatments are based on the positive result of a single randomized controlled trial or inconsistent results of multiple randomized controlled trials (with 1 exception, discussed as follows). The results of published trials and our clinical experience provide the foundation for our specific recommendations for first-line treatments.

First-line Medications. The efficacy of gabapentin, the 5% lidocaine patch, opioid analgesics, tramadol hydrochloride, and tricyclic antidepressants (TCAs) has been consistently demonstrated in multiple randomized controlled trials. Each one can be used as an initial treatment for neuropathic pain in certain clinical circumstances. Opioid analgesics and TCAs generally require greater caution than the other options. For each of these 5 medications, brief reviews of the relevant randomized clinical trials and specific treatment recommendations follow. Treatment recommendations are summarized in **Table 2**.

Gabapentin. There are 8 published double-blind, placebo-controlled randomized clinical trials of gabapentin for chronic neuropathic pain. These studies examined patients with PHN, PDN, mixed neuropathic pain syndromes, phantom limb pain, Guillain-Barré syndrome, and acute and chronic pain from spinal cord injury.[31-38] Gabapentin at dosages up to 3600 mg/d significantly reduced pain compared with placebo; improvements in sleep, mood, and quality of life were also demonstrated in some trials. In 2 trials of PDN and spinal cord injury pain with small sample sizes or relatively lower dosages, evidence of efficacy was more limited.[33,38] On the basis of the results of 2 large randomized trials,[32,34] the FDA approved gabapentin for the treatment of PHN.

The adverse effects of gabapentin include somnolence and dizziness and, less commonly, gastrointestinal symptoms and mild peripheral edema. All of these effects require monitoring and dosage adjustment but usually not discontinuation of the drug. Gabapentin may cause or exacerbate gait and balance problems as well as cognitive impairment in elderly patients, and dosage adjustment is necessary in patients with renal insufficiency. However, its generally excellent tolerability, safety, and lack of drug interactions distinguish gabapentin from most other oral medications used for the treatment of chronic neuropathic pain.

To decrease adverse effects and increase patient adherence to treatment, gabapentin should be initiated at low dosages—100 to 300 mg in a single dose at bedtime or 100 to 300 mg 3 times daily—and then titrated every 1 to 7 days by 100 to 300 mg as tolerated. Although 3 times daily is the target dosage, more rapid titration may be accomplished if most of the daily dose is initially given at bedtime to limit daytime sedation. Target dosages that demonstrated benefits of gabapentin treatment for neuropathic pain ranged from 1800 mg/d (the FDA-approved dosage for PHN) to 3600 mg/d. If only partial relief of pain occurs at 1800 mg/d, titration can be continued up to 3600 mg/d (1200 mg 3 times daily) as tolerated. The final dosage should be determined either by achieving complete pain relief or by the development of unacceptable adverse effects that do not resolve promptly. An adequate trial of gabapentin would include 3 to 8 weeks for titration to allow the development of tolerance to adverse effects, plus 1 to 2 weeks at the maximum tolerated dosage.

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5% Lidocaine Patch. There are 2 published double-blind, randomized, vehicle-controlled clinical trials of the 5% lidocaine patch in patients with PHN.[39,40] In these studies, patients obtained statistically significantly greater pain relief with the 5% lidocaine patch compared with vehicle-controlled patches containing no lidocaine. On the basis of these results, the FDA approved the 5% lidocaine patch for the treatment of PHN. Notably, the efficacy of this treatment has been demonstrated only in patients with PHN and allodynia, and no controlled studies have been conducted for other pain conditions. Anecdotal evidence of a beneficial effect in patients who have other types of neuropathic pain with allodynia has been published.[41]

The 5% lidocaine patch is a topical preparation. In patients with normal hepatic function, blood levels of the drug are minimal, and accumulation does not occur with a dosage schedule of 12 hours on, 12 hours off. Because of this, the 5% lidocaine patch has excellent safety and tolerability, and the only adverse effects involve mild skin reactions (eg, erythema or rash). Systemic absorption from the patch must be considered in patients receiving oral class 1 antiarrhythmic drugs (eg, mexiletine hydrochloride).

Treatment with the 5% lidocaine patch consists of the application of no more than 3 patches daily for a maximum of 12 hours, with the patch applied directly to the area of maximal pain (the FDA-approved dosage for PHN). Titration of the 5% lidocaine patch is not necessary, and an adequate trial would last 2 weeks.

Opioid Analgesics. Five double-blind randomized trials of oral opioid analgesics have been published since 1998. In patients with PHN, controlled-release oxycodone hydrochloride titrated to a maximum dosage of 60 mg/d significantly relieved pain, disability, and allodynia compared with placebo.[42] In patients with PDN, controlled-release oxycodone titrated to a maximum dosage of 120 mg/d significantly improved pain, the performance of daily activities, and sleep compared with placebo; the average dosage of oxycodone in that trial was 37 mg/d (range, 10-99 mg/d).[43] Controlled-release morphine sulfate titrated to a maximum dosage of 300 mg/d was superior to placebo in patients with phantom limb pain.[44]

In a unique 3-period crossover study comparing treatment with opioid analgesics, TCAs, and placebo in patients with PHN, controlled-release morphine sulfate titrated to a maximum dosage of 240 mg/d provided statistically significant benefits for pain and sleep but not for physical function and mood.[45] In that trial, patients preferred treatment with opioid analgesics compared with TCAs and placebo despite a greater incidence of adverse effects and more dropouts during opioid treatment. In a double-blind randomized study that compared 2 different dosages of levorphanol tartrate in patients with a variety of peripheral and central neuropathic pain syndromes, patients receiving the higher dosage reported significantly greater pain reduction, but there were no differences between groups in mood, sleep, or interference with daily activities.[46] In that study, patients with central poststroke pain were the least likely to report improvement; only 30% with this disorder completed the trial. Notably, measures of cognitive function were administered in 2 of these studies, and it was reported that treatment with opioid analgesics did not impair performance.[45,46] Considered together, the results of these 5 studies provide a reliable base of evidence for considering opioid analgesics to be a first-line treatment for neuropathic pain.

The most common adverse effects of opioid analgesics are constipation, sedation, and nausea; these effects most likely contributed to the relatively high withdrawal rates found in the placebo-controlled trials. In elderly patients treated with opioid analgesics, cognitive impairment and problems with mobility can occur, which may contribute to an increased risk of hip fracture. Most patients become tolerant to these adverse effects, although constipation often persists. Regular laxative therapy or switching to transdermal fentanyl citrate may help reduce constipation. Opioid analgesics must be used cautiously in patients with a history of substance abuse or attempted suicide, and accidental death or suicide can occur with overdose. Although patients treated with opioid analgesics may develop analgesic tolerance (ie, a reduction in analgesic benefit with time), in responsive patients a stable dosage can usually be achieved. All patients taking opioid analgesics develop physical dependence (withdrawal symptoms with abrupt discontinuation of the drug or rapid dose reduction) and must be advised not to abruptly discontinue their medication.

The risk that substance abuse, a maladaptive pattern of substance use leading to clinically significant impairment or distress, will develop in patients with neuropathic pain who do not have a history of substance abuse is unknown but probably low. Opioid abuse must be distinguished from the appropriate desire to continue taking medication that effectively relieves pain and from apprehension about not having adequate access to medications that are often difficult to obtain. There is a substantial risk in prescribing opioids to patients with a history of substance abuse; doing so requires very close monitoring. Concerns about causing a substance abuse disorder when there is no history of one do not justify refraining from using opioid analgesics in patients with chronic neuropathic pain.

Numerous short- and long-acting opioid analgesics are available. We hold diverse opinions regarding the algorithm for administering opioids for neuropathic pain. One approach recommended by many of us is to begin treatment with opioid analgesics using a short-acting medication at dosages equianalgesic to the oral administration of morphine sulfate at 5 to 15 mg every 4 hours as needed. Commonly used short-acting opioid analgesics include oxycodone alone and hydrocodone bitartrate and oxycodone in combination with acetaminophen, aspirin, or ibuprofen (a morphine elixir can be used with patients who have difficulty swallowing).

After 1 to 2 weeks of treatment, the patient's total daily dosage of a short-acting opioid analgesic can be converted to an equianalgesic daily dosage of one of the long-acting opioid analgesics such as controlled-release morphine, controlled-release oxycodone, transdermal fentanyl, levorphanol, or methadone hydrochloride. Limited access to short-acting medication for breakthrough pain may be appropriate. Conversion of the patient's treatment regimen from short-acting to long-acting medication may re-

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quire considerable dosage adjustment for 1 to 2 weeks. Once the patient is receiving a stable dosage of a long-acting medication, an adequate trial of an opioid analgesic requires 4 to 6 weeks to assess both pain and function. Pain reduction without improvement in function indicates a need to consider modifying treatment. With careful titration and monitoring, there is no clear maximum dosage of opioid analgesics. However, evaluation by a pain specialist may be considered when morphine sulfate equianalgesic dosages exceeding 120 to 180 mg/d are contemplated. The benefits of levels higher than 180 mg/d in patients with neuropathic pain have not been established in double-blind trials.

Careful documentation and appropriate monitoring of treatment are important for the safe and effective use of opioid analgesics. Model guidelines for the use of controlled substances for the treatment of pain have been adopted by the Federation of State Medical Boards of the United States, and the US Drug Enforcement Administration has recognized that the use of opioid analgesics is appropriate for treating chronic pain.

Tramadol. Tramadol is a norepinephrine and serotonin reuptake inhibitor with a major metabolite that is a μ opioid agonist. There are 2 published double-blind, placebo-controlled randomized clinical trials of tramadol for neuropathic pain, 1 in patients with PDN and 1 in patients with painful polyneuropathy of various causes, including PDN.[47,48] In both trials, tramadol hydrochloride titrated to a maximum dosage of 400 mg/d significantly relieved pain compared with placebo. Beneficial effects of tramadol treatment on allodynia[48] and quality of life[47] were also reported.

The adverse effects of tramadol include dizziness, nausea, constipation, somnolence, and orthostatic hypotension. These occur more frequently when the dosage is escalated rapidly and with concurrent administration of other drugs that have similar adverse-effect profiles. There is an increased risk of seizures in patients treated with tramadol who have a history of seizures or who are also receiving antidepressants, opioids, neuroleptics, or other drugs that can reduce the seizure threshold. Serotonin syndrome may occur if tramadol is used concurrently with other serotonergic medications, especially selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors. Tramadol may cause or exacerbate cognitive impairment in elderly patients, and dosage adjustment is necessary in patients with renal or hepatic disease. Abuse of tramadol is considered rare but has been observed.

To decrease the likelihood of adverse effects and increase patient adherence to treatment, tramadol should be initiated at low dosages—50 mg once or twice daily—and then titrated every 3 to 7 days by 50 to 100 mg/d in divided doses as tolerated. The maximum dosage of tramadol hydrochloride is 100 mg 4 times daily (in patients older than 75 years, 300 mg/d in divided doses), and an adequate trial requires 4 weeks.

Tricyclic Antidepressants. The first medication category that proved effective for neuropathic pain in placebo-controlled trials was TCAs.[25-28] Although clinical trials of patients with HIV sensory neuropathy,[49,50] pain from spinal cord injury,[51] and cisplatin-induced neuropathy[52] found little benefit of treatment with amitriptyline hydrochloride when compared with placebo, an apt summary of the overall efficacy of TCAs in neuropathic pain is provided by the title of a review by Max.[53]

The primary problem with the use of TCAs is their adverse-effect profile; TCAs must be used cautiously in patients with a history of cardiovascular disease, glaucoma, urinary retention, or autonomic neuropathy. Almost 20% of patients treated with nortriptyline after a myocardial infarction developed adverse cardiac events in a recent study.[54] Consequently, a screening electrocardiogram to check for cardiac conduction abnormalities is recommended before beginning treatment with TCAs, especially in patients older than 40 years. As with opioid analgesics, TCAs must be used cautiously when there is a risk of suicide or accidental death from overdose. They may block the effects of certain antihypertensive drugs (eg, clonidine or guanethidine), and they interact with drugs metabolized by cytochrome P4502D6 (eg, cimetidine, phenothiazines, and class 1C antiarrhythmics). All SSRIs inhibit cytochrome P4502D6, and to prevent toxic concentrations of TCAs in the plasma, caution must be exercised in the concomitant administration of TCAs and SSRIs and when switching from one drug class to the other. In elderly patients, TCAs may cause balance problems and cognitive impairment. Milder adverse effects of TCAs include sedation, anticholinergic effects (eg, dry mouth or constipation), postural hypotension, and weight gain.

Although most clinical trials of TCAs for neuropathic pain have examined amitriptyline, this drug is not recommended in elderly patients because of the risk of significant adverse events. Nortriptyline and desipramine hydrochloride have fewer adverse effects and are generally better tolerated than amitriptyline. In a recent randomized double-blind trial, nortriptyline was found to provide equivalent analgesic benefits in patients with PHN when directly compared with amitriptyline but was better tolerated.[55]

Patients must understand that TCAs have an analgesic effect that has been demonstrated to be independent of their antidepressant effect. To decrease adverse effects and increase patient adherence to treatment, TCAs should be initiated at low dosages—10 to 25 mg in a single dose at bedtime—and then titrated every 3 to 7 days by 10 to 25 mg/d as tolerated. Although the analgesic effect of TCAs has been thought to occur at lower dosages than the antidepressant effect, there is no systematic evidence of this. However, some data are consistent with a dose-response relationship; TCAs should be titrated to dosages of 75 to 150 mg/d as tolerated. If a blood level of approximately 100 ng/mL of the active drug and its metabolite is not found at dosages of 100 to 150 mg, titration can be continued further with caution. Blood levels of 500 ng/mL or higher of the active drug and its metabolite are associated with toxicity, and for titration higher than 100 to 150 mg/d, blood levels should be monitored and an electrocardiogram performed. An adequate trial of a TCA would last 6 to 8 weeks with at least 1 to 2 weeks at the maximum tolerated dosage.

Selecting a First-line Medication. Medication acquisition costs vary greatly by geographic region, insurance

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plan, industry health plan contracts, and availability of pharmaceutical company programs for patients without drug benefit plans. Physicians should become as familiar as possible with the acquisition costs of the medications they prescribe and with the reimbursements provided by their patients' insurance plans. Doing so will not only benefit the finances of their patients but will also maximize adherence to treatment recommendations. Consideration should be given to the availability of generic versions of medications used in treating chronic neuropathic pain. Tramadol, TCAs, and some opioid analgesics are available in generic forms with acquisition costs considerably lower than the 2 first-line medications that are still protected by patent: gabapentin and the 5% lidocaine patch.

Tricyclic antidepressants must be used with extreme caution in elderly patients because of the risk of toxic adverse effects to the heart and anticholinergic adverse effects. In addition, gabapentin, opioid analgesics, tramadol, and TCAs must all be used with caution in older patients because of the risk of falls and cognitive impairment.

Tricyclic antidepressants have numerous contraindications, especially in patients with cardiovascular disease, because of the risks of conduction defects, arrhythmias, tachycardia, stroke, and acute myocardial infarction. In patients with renal insufficiency, the dosage of gabapentin or tramadol must be adjusted; in patients with hepatic disease, dosage adjustment of tramadol is necessary. Opioid analgesics must be used with caution in patients with a history of substance abuse.

Tricyclic antidepressants may be especially useful for treating depression in patients with chronic pain, but the risk of intentional overdose must be kept in mind; there is a much higher risk of suicide with TCAs compared with other antidepressants. In addition, many patients with chronic pain have disturbed sleep, and trials of gabapentin and TCAs have demonstrated improvements in this area.

Many patients with neuropathic pain also have nonneuropathic pain (eg, osteoarthritis), and opioid analgesics and tramadol have demonstrated efficacy in the treatment of both types. It has been suggested that TCAs should be used in treating constant pain and that carbamazepine-like anticonvulsants should be used for lancinating pain. However, the results of the randomized controlled trials of TCAs and anticonvulsants that have systematically assessed pain quality show no evidence of a differential treatment response.

Onset of pain relief is faster with the 5% lidocaine patch, opioid analgesics, and tramadol than with gabapentin or TCAs. This is primarily because gabapentin and TCAs require slower titration to effective dosages owing to their adverse effects. Gabapentin, the 5% lidocaine patch, and opioid analgesics all have fewer adverse drug interactions than tramadol or TCAs.

Sequential and Combination Treatment With First-line Medications. The percentage of patients with neuropathic pain who do not respond to 1 of these 5 first-line medications but who then obtain satisfactory pain relief from a different one is unknown. Even within a class of medication, some patients fail to respond to one medication but then respond to another. In a crossover trial comparing amitriptyline and nortriptyline in 31 patients with PHN, 5 patients had moderate or severe pain when administered nortriptyline but none or mild pain with amitriptyline, and 4 patients had the opposite pattern of response.[55] Current understanding of the pathophysiologic mechanisms of neuropathic pain is consistent with the existence of multiple pain mechanisms, each of which may respond differently to medications with different mechanisms of action.[13-16] Therefore, there is both an empiric and theoretical basis for recommending that patients who do not respond to 1 of these 5 first-line medications be treated with another one.

It is common for patients to have a partial response to these medications, and combination treatment should be considered when this occurs. No studies have systematically examined the efficacy of various possible combinations of these 5 medications compared with monotherapy. Despite the lack of controlled data, combinations of 2 or more of these first-line medications can be recommended when patients have a partial response to a single one or at the beginning of treatment, either to increase the likelihood of a beneficial response or when a medication that requires titration to reach an effective dosage is also being used. Disadvantages of combination therapy include an increased risk of adverse effects as the number of medications is increased and difficulty identifying which of several medications is responsible for the adverse effects.

Second-line Medications. When patients do not have a satisfactory response to treatment with the 5 first-line medications alone or in combination, several medications can be considered second-line. Because these second-line treatments are used less often by physicians and fewer trials have examined their efficacy, their use is not described in detail. Recommendations for second-line medications are based on positive results from a single randomized controlled trial or inconsistent results from multiple randomized controlled trials, with 1 exception.

Other Anticonvulsant Medications. Lamotrigine is the 1 second-line pharmacologic treatment for which there is evidence of efficacy based on consistent results of multiple randomized controlled trials for HIV sensory neuropathy,[56,57] PDN,[58] and central poststroke pain[59] as well as in a subgroup of patients with incomplete spinal cord lesions in a trial of patients with pain from spinal cord injury.[60] We do not consider lamotrigine a first-line treatment for neuropathic pain because of the slow and careful titration required and the risk of both severe rash and Stevens-Johnson syndrome associated with its use.

Carbamazepine has a well-established beneficial effect for trigeminal neuralgia[24,30] and is approved by the FDA for the treatment of this neuropathic pain syndrome. In patients with PDN, some evidence exists for a beneficial effect of carbamazepine, but results from studies of phenytoin are inconsistent; these clinical trials were conducted more than 20 years ago and do not meet current methodological standards.[24,26-28] On the basis of clinical trials of anticonvulsants for chronic neuropathic pain,

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lamotrigine and carbamazepine can be recommended for patients who have not responded to an adequate trial of gabapentin when treatment with an anticonvulsant is sought.

Evaluation of the role of other second-generation anticonvulsants (eg, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide) for the treatment of neuropathic pain must await publication of the results of randomized placebo-controlled trials. Although several anticonvulsant medications block sodium channels, available anticonvulsants have different and often multiple mechanisms. Therefore, nonresponse to 1 anticonvulsant does not necessarily predict nonresponse to the category as a whole.

Other Antidepressant Medications. Selective serotonin reuptake inhibitors have fewer adverse effects and are generally better tolerated than TCAs. In studies of patients with PDN, paroxetine and citalopram were associated with statistically significantly greater pain relief than placebo, whereas fluoxetine hydrochloride was found to be no more effective than placebo.[25-28] Sustained-release bupropion hydrochloride was studied in a controlled trial of patients with different peripheral and central neuropathic pain syndromes and found to provide statistically significant pain relief compared with placebo.[61] In a recent randomized, 3-period crossover trial of venlafaxine hydrochloride and imipramine hydrochloride in patients with painful polyneuropathy, both antidepressants demonstrated superior pain relief compared with placebo but did not differ from each other.[62] A placebo-controlled crossover trial of 13 patients with chronic neuropathic pain following breast cancer surgery failed to find a significant benefit of venlafaxine vs placebo for the primary end point (daily pain diary ratings) but did find greater relief associated with venlafaxine treatment for 2 secondary pain end points.[63] Results of these clinical trials indicate that bupropion, citalopram, paroxetine, and venlafaxine can be recommended for patients who have not responded to an adequate trial of nortriptyline (or another TCA) when additional treatment with an antidepressant is being considered.

Beyond Second-line Medications. Other medications sometimes used for the treatment of patients with neuropathic pain include capsaicin, clonidine, dextromethorphan, and mexiletine. According to our clinical experience and the inconsistent results of clinical trials, these medications may occasionally be effective in individual circumstances.

Future Needs

Treatment duration in most clinical trials of neuropathic pain has typically been 8 weeks or less; therefore, durability of pain relief and the long-term safety and tolerability of treatment are unknown. With chronic disorders, it is important to consider the long-term cost-effectiveness of treatment.[64] Although the development of new treatments for neuropathic pain is continuing rapidly,[65,66] few clinical trials have directly compared medication options.[45,55,62] Such comparisons will make it possible to determine not only whether treatments vary in their efficacy, safety, and tolerability but also, when conducted in the same patients, the extent to which treatment response with one medication predicts response to others.[45] Systematic evaluation of combination treatment is needed as well. Although a large percentage of patients with neuropathic pain are currently treated with 2 or more of the first- and second-line medications discussed, little is known about which patients are most likely to benefit from combination treatment and whether such treatment has additive or synergistic effects. Morever, because combinations of pharmacologic and nonpharmacologic treatments have received little study in patients with neuropathic pain, it is unknown, for example, whether physical therapy or psychological treatment provides an additional benefit beyond that obtained from pharmacologic treatment alone.

CONCLUSIONS

Interest in the mechanisms and treatment of chronic neuropathic pain has increased during the past several years, and this is likely to result in significant treatment advances in the future. These advances will make it possible to go beyond the determination of whether treatment is effective to the identification of what treatments are most effective for which patients.[13,67] Progress in basic science will lead to a greater understanding of the pathophysiologic mechanisms of neuropathic pain. Important goals for clinical research are to devise methods for reliably identifying specific mechanisms in individual patients and to target treatment to them.[13-17] Greater attention should also be paid to developing preventive interventions for patients who are at risk for chronic neuropathic pain, including patients undergoing breast cancer surgery,[68] those with herpes zoster,[69] and those with diabetes.[70]

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